15

Computer-Aided Detection and Diagnosis

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Computers are especially suited to help the physician collect and process clinical information and remind him of diagnoses which he may have overlooked.

Robert S. Ledley and Lee B. Lusted
Science 1959 **Q1**

15.1 Introduction

After the world's first general purpose computer was built in 1940s, the idea of using computers to assist physicians in medical decisions became an increasingly enticing possibility **Q2** (Ledley and Lusted, 1959). Since then, computer applications have become pervasive in daily life, and their use in the field of medicine has grown from strength to strength. Given the largely digital nature of information in images, the field of medical imaging is particularly well placed to leverage on the processing power of computers to enhance existing work processes.

The task of medical image interpretation involves a complex series of tasks which include detection of an abnormality, description of the characteristics of a lesion, diagnosis of a specific disease entity or syndrome, and evaluation of the extent of pathology to aid prognostication. The use of computers to facilitate or perform any or all of these interpretative steps was first described in the 1960s (Lodwick et al., 1963), and continues to grow at a rapid pace, catalyzed by major advances in processing power, the widespread availability of high-resolution volumetric image data sets, improved software algorithms, and the proliferation of digital imaging technology. This exciting field was initially described as Computer-aided diagnosis (CAD), a term which has since been broadened to include the use of computers in the detection of abnormalities, characterization of lesion features, and detection of changes over time.

Early CAD work centered on developing systems could perform comparably or even better than physicians. However, it was subsequently recognized that a useful CAD system did not have to replicate or replace the physician. Instead, CAD could still add value by playing a complementary role. This paradigm shift recognized that the true value of CAD was in the synergistic combination of the clinical competence of a physician and the consistent capability of a computer, bringing along the associated benefits such as reduction in image reading time and interobserver variability. CAD is now a major research subject in the field of medical imaging (Erickson and Bartholomai, 2002; Khorasani et al., 2006; Doi, 2007).

15.2 CAD in the Medical Image Review Process

15.2.1 Overview of the Medical Image Review Process

The task of medical image interpretation begins after image data have been acquired (e.g., by a CT or MRI scanner, etc.) and appropriate quality control checks performed. The process of image interpretation by a radiologist is a complex and often iterative process during which information obtained from the images and other relevant medical data (e.g., presenting symptoms of the patient, laboratory results, past medical history) are combined to facilitate a conclusion about whether pathology exists, what the condition is, and how extensive the disease is. This in turn facilitates a clinical decision on the appropriate medical management.

The overall process of medical image interpretation, while complicated, can be simplified as shown in Figure 15.1. The first step in the image interpretation process is *detection*, which is perception of an abnormality in the image (e.g., is there a nodule in the lung?). The next step is *description*, during which the radiologist characterizes the abnormality in order to ascertain its nature (e.g., Does the lung nodule have speculated edges? Is the nodule calcified? Where is the nodule located?). Following description, the radiologist goes on to provide a *diagnosis*, or more often, a list of differential diagnoses based on probability (e.g., spiculated lung nodule, likely malignant, most probably bronchogenic carcinoma). The final step involves providing a *prognosis* based on the likely condition, and includes the evaluation of other imaging findings in order to determine the extent, severity and likely outcome of the condition (e.g., bronchogenic carcinoma with bilateral hilar nodes, and metastases seen in the ribs, left humerus and liver—stage 4 disease with poor prognosis). This process of image interpretation is often not as simple and linear as depicted above, and may involve several parallel or iterative steps, depending on whether multiple pathologies coexist, and whether the diagnosis is already known.

15.2.2 Types of CAD

Given the myriad potential applications of computers in image interpretation, there is understandably a correspondingly wide range of descriptive terms for CAD used in literature. For simplicity, the abbreviation “CAD” in this chapter refers generically to all the potential applications of computers to aid detection, description, diagnosis and prognosis. Each type of CAD has different roles and capabilities, and some CAD systems are a combination of more than one functional type. Regardless of which existing CAD nomenclature one may be familiar with, it is useful to keep in mind how the various CAD systems facilitate the basic steps in the overall image interpretation process, which in turn is heavily dependent on the clinical context. Using the simplified image interpretation process outlined above, the various types of CAD systems and their potential applications may be classified as shown in Figure 15.2.

FIGURE 15.1 Simplified representation of the medical image interpretation process.

15.2.2.1 Computer-Aided Detection

Computer-aided detection (CADe) systems are designed to identify potentially abnormal findings in an image. Common examples include the use of CADe systems to identify suspicious microcalcifications in mammograms, or detect colonic polyps in CT colonography studies. Such CADe systems are typically used as prompting devices, marking locations of suspected abnormalities via an overlay on a medical image.

15.2.2.2 Computer-Aided Characterization

Computer-aided characterization (CAC) systems are designed to provide accurate and reproducible descriptions of a lesion in a medical image. These characteristics are usually obtained concurrently as part of lesion detection. For example, in the process of detecting a lung nodule on a CT scan, the size and edges of the nodule would have already been characterized, along with the volume and other features such as average Hounsfield values and relationships to adjacent structures. CAC systems are also useful in rapidly evaluating multiple complex data sets over a period of time, such as the enhancement characteristics of a breast nodule on MRI (e.g., time to peak signal intensity and the rate of washout of gadolinium). The characteristics of the lesion obtained through CAC can then be used both for diagnosis and prognostication of a disease process.

15.2.2.3 Computer-Aided Diagnosis

Computer-aided diagnosis (CADx) systems are designed to process a specific finding and describe it accurately, characterize the likelihood of a specific diagnosis (e.g., likelihood of malignancy), provide differential diagnoses in order of probability, or recommend a clinical action. In mammography, CADx is able to characterize clusters of microcalcifications based on predetermined criteria in order to provide the probability of malignancy, aiding the radiologist in deciding on the need for a tissue biopsy. Some CADx systems are able to provide a more specific and definitive diagnosis, and the utility of such CADx systems is usually restricted to clinical scenarios where a detected abnormality has a very limited list of possible differential diagnoses, for example, the presence of distinct filling defects within the pulmonary arteries on a CT pulmonary angiogram study are almost always due to pulmonary embolism.

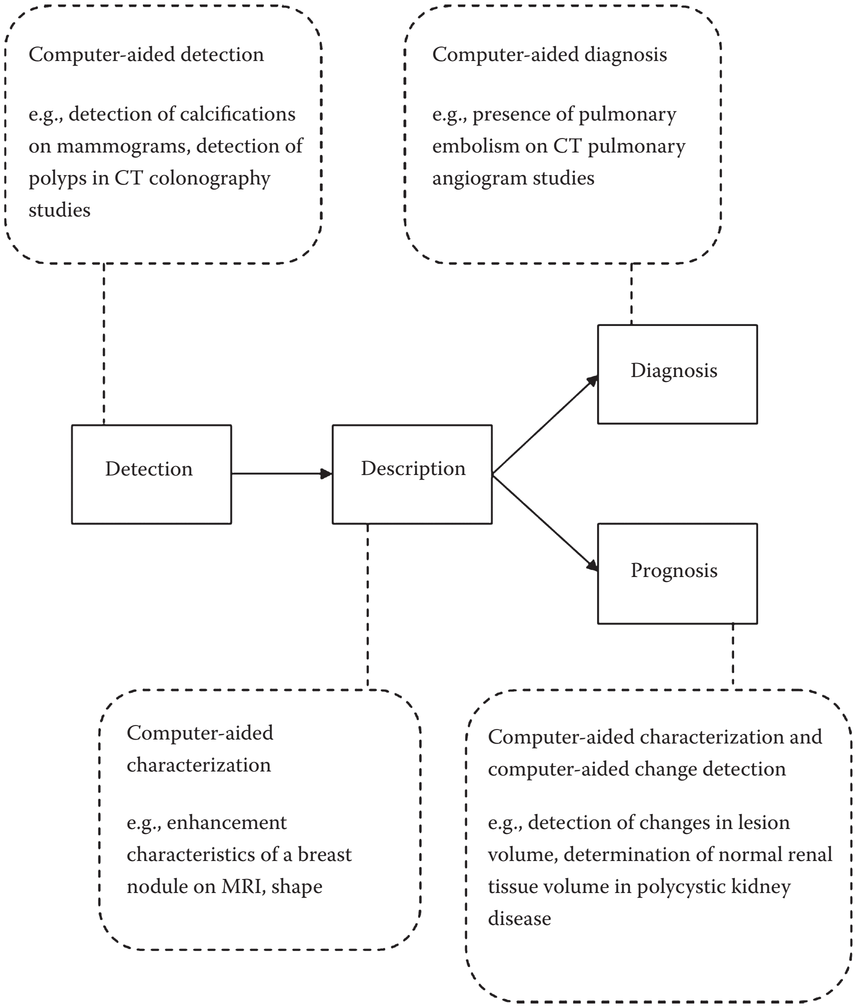

FIGURE 15.2 Potential roles of CAD in the medical image interpretation process.

15.2.2.4 Computer-Aided Change Detection

Computer-aided change detection (CACD) systems are designed to detect changes in sequential studies of the same anatomical region, quantify the amount of change, or characterize the significance of the change. An example of CACD applied to a common clinical problem is the determination of changes in brain tumor volume on MRI over time to evaluate disease status and response to treatment. More advanced CACD systems are expected to be able to evaluate variable degrees of change in multiple lesions for the same patient, and provide an overall picture of disease status. Such CACD systems have the potential to provide valuable information regarding response to treatment in clinical trials.

15.3 Goals of CAD

Having described the overall imaging interpretation process and the potential roles of CAD in enhancing the existing workflow, the goals of CAD and the case for CAD utility will be presented. Key issues in this discussion include what value computers add to the process, and conversely, what role a radiologist can continue to play in the age of CAD. The relationship between humans and computers should ideally be based on a synergistic model, capitalizing on the strengths of each while minimizing their respective weaknesses, all for the benefit of the patient. Computers are best suited for repetitive tasks involving objective information in large data sets. On the other hand, the physician is better positioned to integrate medical information from multiple sources, recognize various patterns of clinical syndromes, and evaluate the relevance of an abnormality in a given clinical context. In other words, computers have an edge in the “science” of medicine, while physicians have the lead in the “art” of medicine.

15.3.1 Consistent Detection of Imaging Abnormalities

Humans make errors during image interpretation due to factors such as fatigue, information overload, inexperience and environmental conditions. Computers, while not free from making mistakes, are able to rapidly process large volumes of imaging data in a more consistent fashion. The more specific the abnormality and focused the detection task, the better the computer algorithm for lesion detection is likely to be. These considerations are especially applicable to medical screening, where large numbers of imaging studies are read, the majority of which are normal. Screening examinations (e.g., mammography or CT colonography) that have standardized formats and few pathologies of interest with limited appearances are particularly suited for CADe. This area of CAD application is currently the most well-researched and developed.

15.3.2 Accurate and Reproducible Description of Imaging Features and Abnormalities

After detection, a lesion needs to be accurately characterized in terms of anatomic extent, imaging properties (e.g., size, shape, and other physical characteristics), and other features of interest (e.g., contrast enhancement, appearance of margins, etc.). Computers are better suited for performing accurate measurements and feature descriptions in a reproducible manner over an extended period of time. A clear example of this would be measurement of changes in size of lung nodules. This was previously dependent on manual measurements of lesion diameter which was prone to interobserver and intraobserver variation. Automated calculations of nodule volume were more reproducible and better at picking up small changes in lesion size. Quantifiable lesion characteristics can be used to generate lesion descriptors that enable CAD algorithms to accurately classify lesions (diagnosis) and determine disease status (prognosis).

15.3.3 Diagnosis of Imaging Abnormalities

A final diagnosis for patient management is derived not only from a single medical imaging study, but is instead arrived at after consideration of multiple data sources, including other imaging studies, comparisons with prior imaging examinations, and other clinically relevant information (e.g., demographic data, clinical history, findings on physical examination, other test results, etc.). While computers are able to quickly search and retrieve information from vast databases, automation of this complex synthesis of medical information to arrive at a specific diagnosis remains a formidable challenge. Hence, the process of combining these multiple sources of information, and deriving a list of differential diagnoses in order of probability that is customized for a particular patient within a specific clinical context is currently one better performed by a physician.

15.4 Techniques and Components of CAD

While several types of CAD systems exist, the fundamental components of a typical CAD system are similar, and are illustrated in Figure 15.3.

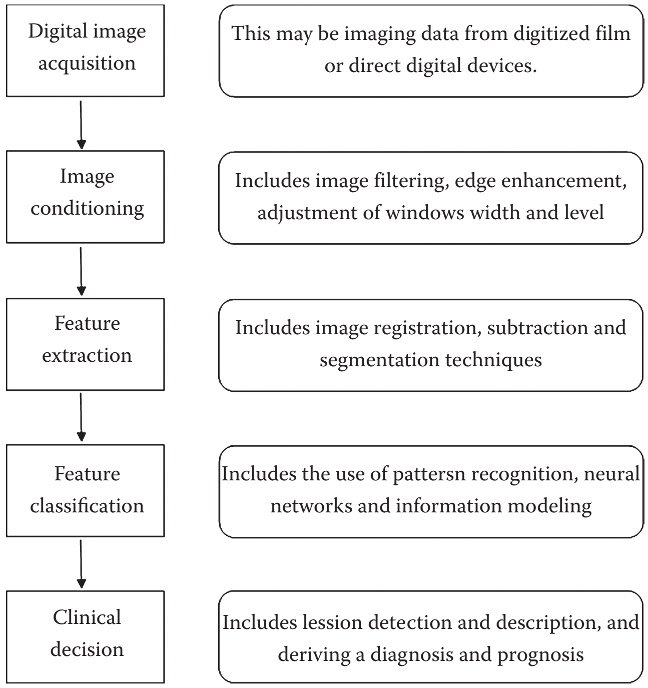

FIGURE 15.3 Functional components of a typical CAD system.

15.4.1 Digital Image Acquisition

The digital image data may be acquired from a variety of sources such as computed or digital radiography devices, ultrasound machines, gamma cameras, CT scanners, and MRI machines. Another method of obtaining usable image data includes digitizing images previously obtained with conventional radiography techniques (e.g., film-screen techniques), although some loss of information is expected through the digitization process. High-quality image data is critical to successful utility of any CAD system. Notwithstanding the different possible sources for the digital image, the basic prerequisites for the image are sufficient spatial resolution, good contrast resolution, high signal-to-noise ratio, and minimal image artifact. For volumetric data sets obtained with multidetector CTs, thin slices with isotropic voxels are preferred, although one must balance the radiation burden to the patient with the need for thin slices.

15.4.2 Image Conditioning

The aim of image conditioning is to optimize key attributes of digital images to enhance subsequent data manipulation and interpretation by the CAD system. Image conditioning techniques include the application of basic filters to image data and enhancement of features (e.g., edges) to increase lesion conspicuity. Excessive image conditioning may create artifacts in images that negatively impact CAD interpretation, resulting in increased false-positive instances.

15.4.3 Feature Extraction

Feature extraction is the process where key characteristics of an image such as an anatomical region or suspected lesion(s) are isolated from nonessential background information in the data set. Techniques available for feature extraction range from simple thresholding, segmentation, registration and subtraction, to complex shape analysis. Segmentation is a process of partitioning a digital image into various regions in order to facilitate subsequent analysis. An example would be segmentation of the colon in a CT colonography study so that only pixels related to the colon are subjected to subsequent analysis for the presence of polyps. Image subtraction highlights differences between imaging studies, and is typically used to highlight changes of a lesion over time. Image registration, the precise alignment of comparison images, is a key prerequisite for image subtraction. Modern techniques enable not only registration of images from similar studies, but also allow alignment of studies with differing contrast properties (e.g., registration of MRI and CT images).

15.4.4 Feature Classification

After relevant image features are extracted, classification ensues to derive a usable output (e.g., likelihood of malignancy, differential diagnoses) from the analysis of the features. This enables the physician to make sense of the CAD outputs to arrive at a clinical decision. The process of classification in CAD systems may incorporate rules based on *a priori* knowledge of disease features and prevalence, pattern recognition, and other probability modifiers.

15.4.4.1 Pattern Recognition and Neural Networks

Human interpretation of medical images is usually based on recognizing patterns of radiological findings and their respective associations with different diseases. Computers can mimic this pattern recognition process through the use of statistical methods and neural networks that facilitate machine learning, leveraging on vast databases of medical information (Coppini et al., 2003; Döhler et al., 2008; Suzuki, 2009).

15.4.4.2 Information Modeling and Probability

The accuracy of diagnosis is not only a function of the information in the images, but also requires consideration of the medical context of the patient who underwent the imaging study. This medical context takes into account *all* disease entities that might exist in the patient, along with their associated probabilities. Probabilities are dependent on specific information that is unique to each patient, and general information about various disease probabilities. These are factors that a physician takes into account when formulating a final impression for each imaging study. While attempts have been made to create computer algorithms to take these additional data inputs into account, the challenge remains to create CAD applications that are not only reliable in specific situations (e.g., screening), but are also applicable to diverse clinical settings.

15.4.5 Clinical Decision

After classification of the features of a detected abnormality, the CAD system provides a final usable output to facilitate the clinical decision by the evaluating radiologist. Depending on the clinical context for the particular patient who underwent the imaging study, the final output may include detection of an abnormality, description/characterization of a known abnormality, providing a diagnosis or list of differential diagnoses, or evaluation of disease progression.

15.5 Utility of CAD

15.5.1 Modes of CAD Utility

CAD devices or systems, when utilized in the image interpretation process by a physician, can be applied either as a first reader, second reader, or concurrent reader. Each mode of CAD application has its attendant advantages and disadvantages, and the optimal method of using CAD continues to be an area that requires more research.

15.5.1.1 First Reader CAD

In the first reader mode, the physician reviews only regions or findings marked by the CAD device. Imaging findings not highlighted by the CAD system are not reviewed by a physician. The main benefit of such a CAD system is an anticipated reduction in time required to review medical images, a proposition that is increasingly attractive in an era of multidetector CT where the number of images per study can range in the thousands. However, such a CAD system would need to have a performance at least equal, if not better, than that of a physician reviewer. To date, no CAD system has been approved for first reader use.

15.5.1.2 Second Reader CAD

When CAD is used as a second reader, the physician first does a full interpretation of the imaging study without CAD, and then reinterprets the study with the CAD system. The computer provides a "second opinion," but the responsibility for the final evaluation and diagnosis is still made by the physician in all cases. This method of using CAD systems is analogous to using a spelling or grammar checking function in word processing software. This second reader mode is currently the most common clinical application of CAD systems. A key concern regarding the use of CAD in second reader mode is the extra time required to review CAD outputs, a time burden which could become excessive if the CAD system generates a large number of false-positive detections.

15.5.1.3 Concurrent Reader CAD

For the concurrent reader application of CAD, the physician performs a single-pass complete interpretation of the imaging study in the presence of CAD markings. This method of CAD utility potentially offers a way to reap the benefits of CAD while mitigating the time burden of reviewing extra CAD outputs. However, this method removes the first-cut independent review of the images by the physician, a step which is known to pick up lesions not otherwise detected by a CAD system. There is also concern that routine application of concurrent reader CAD may reduce reader vigilance by distracting the physician from performing an unbiased systematic review of the images.

15.5.1.4 Automated Computer Diagnosis

It is important to differentiate CAD from Automated Computer Diagnosis (ACD). In ACD, the final diagnosis is derived from computer algorithms alone, without human intervention. With CAD, computer performance does not necessarily have to be comparable to or exceed that of physicians, but need only be complementary. On the other hand, ACD must have a performance equal or better to that of humans in all possible clinical scenarios, as the images would not be viewed by a physician at all. To date, there is no approved software for clinical utility as an ACD system.

15.5.2 Limitations of CAD Systems

CAD performance (e.g., sensitivity, specificity, accuracy, etc.) is dependent on the underlying algorithm and type of training data set used, which are tailored for specific clinical scenarios. Inappropriate application of CAD to different clinical contexts (e.g., a patient population with different types or likelihood of disease, using a second reader CAD as a first reader, etc.) can negate the strengths of CAD and decrease physician performance. For example, a CAD system for detecting colonic polyps that was developed using CT images from a symptomatic population may not necessarily be applicable to CT images of a healthy asymptomatic population.

As with any test, there is a need to balance between sensitivity and specificity, and improving the sensitivity of CAD systems would also often increase the false-positive rate. CAD systems which routinely generate a large number of false-positive image annotations would in time be ignored by the reviewing radiologist, thus negating the expected benefits of the CAD system. Receiver Operating Characteristic (ROC) curves are a useful method to evaluate the accuracy of a CAD system and compare the results of different CAD systems. ROC curves are generated from a range of sensitivity and corresponding specificity values, and therefore can incorporate different decision thresholds that a radiologist may choose in using a CAD system. The area under the ROC curve (AUC) provides a useful summary of the accuracy of the test, and ranges in value from 0.5 (results attributable to chance, with no additional discriminatory value compared to a coin toss) to 1.0 (perfect discrimination or accuracy).

When introducing CAD systems, the learning curve and adjustment period for users (estimated to take weeks to years) needs to be taken into account. Temporary changes to workflow (e.g., transiently reducing the number of reads per session) may be required to decrease the impact of this adjustment period on clinical service delivery. The expected benefits of CAD are also dependent on whether the systems are deployed for use by subspecialty expert radiologists (e.g., body imaging radiologists who routinely review large volumes of CT colonography studies and would therefore already have a high sensitivity and specificity for lesion detection) as compared to general radiologists (who may only occasionally be required to review a CT colonography examination). CAD systems may also elicit varying reactions from different users, and thus have an unexpected impact on the interpretation process and reading time.

15.6 Current Applications of CAD

15.6.1 Breast Imaging

After cancers of the skin, breast cancer is the most frequently diagnosed cancer in women. Breast cancer screening is therefore a major public health initiative globally. Mammographic screening for breast cancer involves evaluating large numbers of studies, most of which are expected to be normal, for a specific abnormality (breast cancer) which has a relatively limited range of appearances. The false-negative rate for mammographic detection of breast cancer ranges from about 10% to 25% (Destounis et al., 2004) and there is significant interobserver variability in the evaluation of breast imaging studies (Skaane et al., 1997). Prior attempts to address such issues and increase the accuracy of mammographic screening include the employment of "double reads" where second radiologist independently reviews mammographic images for abnormalities, a role which may potentially be played by CAD in a second reader mode (Helvie, 2007). These characteristics of mammographic screening for breast cancer make it particularly suited for CAD deployment, and it is therefore not surprising that mammography was the first major area where CAD usage was adopted.

The first FDA approved CAD products were for mammography in 1998. Modern CAD systems analyze digitized or digital mammographic images to find features of breast cancer such as clustered microcalcifications, masses and architectural distortion. The methods and challenges in detecting and characterizing such features of breast cancer have been recently discussed (Giger et al., 2008; Elter et al., 2009). Suspicious mammographic **Q3** features are then highlighted to the radiologist for review. The radiologist then makes a final decision regarding the likely nature of the lesion and further management as required. It is important to note that mammographic CAD systems are currently designed for use as a second reader, which requires the radiologist to first review the images independent of the CAD system, with a subsequent "second look" with the CAD markings. The utility of current mammographic CAD systems as either a first or concurrent reader is not recommended.

To date, no randomized controlled trials have been done to document changes in patient survival from the use of CAD in mammography. Surrogate end points (e.g., cancer detection rate, stage of cancer, frequency of interval cancers, change in recall rate etc) have been used to evaluate CAD performance. Overall, CAD trials have generally, but not always, shown improvements in cancer detection (Helvie, 2007). Most studies show that incremental cancer detection by CAD systems are mainly restricted to ductal carcinoma-*in-situ* (a noninvasive type of cancer). It remains

TABLE 15.1 Summary of Results of Recent Studies of CAD Systems for Detection of Breast Cancer in Screening Mammography

Investigators (Year)	Number of Exams	Change in Cancer Detection Rate (%)	Change in Recall Rate (%)
Gromet (2008)	231,221	+1.9	+3.9
Fenton et al. (2007)	429,345	+1.2	+30.7
Dean et al. (2006)	9520	+10.8	+26.0
Ko et al. (2006)	5016	+4.7	+15.0
Morton et al. (2006)	21,349	+7.6	+10.8
Birdwell et al. (2005)	8682	+7.4	+8.2
Cupples et al. (2005)	27,274	+16.1	+8.1
Gur et al. (2004)	115,571	+1.7	+0.1
Freer et al. (2001)	12,860	+19.5	+19.0

uncertain whether such additional detections will affect overall patient outcomes in the long term. Single reads of mammographic studies with CAD have also shown promise as a viable alternative to routine double reading (Gilbert et al., 2008; Gromet, 2008). Excellent reviews of the useful role of CAD in screening mammography were recently published (Helvie, 2007; Birdwell, 2009). A summary of recent CAD trials in the detection of breast cancer in screening mammography is given in Table 15.1.

CAD has also been used to facilitate evaluation of lesions on breast MRI, including lesion morphology and the complex task of characterizing lesion enhancement kinetics (e.g., rate of enhancement and washout). CAD systems have also been developed for use with breast ultrasound in order to analyze morphologic features of breast lesions (e.g., size, shape, orientation) as well as detect lesion boundaries.

Possible future trends for CAD in breast imaging include the development of CAD systems that incorporate information from multiple mammographic images (e.g., comparisons with the contralateral breast, comparison with prior images of the same breast, correlation with different projections of the same breast region), different image sources (e.g., concurrent CAD evaluation of mammogram, ultrasound and MRI images to provide an integrated CAD output) and incorporation of newer breast imaging modalities such as digital breast tomosynthesis, contrast-enhanced digital subtraction mammography, breast PET, and breast CT.

15.6.2 Chest Imaging

The detection and evaluation of lung nodules is a very common clinical challenge encountered by radiologists. This has become a more pressing problem with the advent of multidetector CT, which has not only increased the number of images requiring review by a physician, but also resulted in a vast number of small pulmonary nodules of uncertain significance being detected on a regular basis. Furthermore, lung cancer, which accounts for the most cancer-related deaths in both men and women in the United States, often begins as a pulmonary nodule. Lung CAD has therefore been dominated by applications in pulmonary nodule detection and volumetry (Li, 2007; Marten and Engelke, 2007).

CAD systems for use with chest radiography and CT to detect lung nodules were first approved by the FDA in 2001 and 2004, respectively. Because CT has been shown to have a higher sensitivity for detection of lung nodules than conventional chest radiography, the majority of CAD development for chest imaging in recent years have focused on thoracic CT. Lung nodule CAD algorithms capitalize on the inherent high contrast between nodules and the surrounding lung tissue to facilitate detection. Overall, current lung CAD systems for nodule detection on CT have varying reported true positive rates ranging from about 70% to over 90% with a false-positive rate of about 0.1 to 1 nodule per section (Giger et al., 1994; Armato et al., 1999; Lee et al., 2001; Awai et al., 2004). As with breast imaging CAD, current lung nodule CAD systems should be used in a second reader capacity only. To date, no prospective outcome-based trials have been published evaluating the performance of CAD for detection of nodules in CT. A summary of recent studies on CAD utility in nodule detection is given in Table 15.2.

CAC of lung nodule features on CT such as nodule volume, lesion margins, lesion density, presence of calcifications, and enhancement characteristics allow more accurate and reproducible descriptions of lung nodules. Such characterization allows for improved follow-up of indeterminate lung nodules, and enables better evaluation of response to treatment. For example, manual two-dimensional measurements of nodules less than 5 mm in size can vary by as much as ±1 mm, which translates to a greater than 75% difference in volume. This variability is reduced by computer-aided volumetry, which would allow earlier detection of real (but small) changes in nodule size.

Current challenges in lung CAD systems for nodule detection and characterization include evaluation of lesions which do

TABLE 15.2 Summary of Results of Recent Studies Evaluating CAD Impact on Detection of Pulmonary Nodules by Radiologists for CT Thorax Studies

Investigators (Year)	Number of CT Exams	Results
White et al. (2008)	109	CAD increased AUC from 86.7% to 88.7%.
Hirose et al. (2008)	21	CAD improved mean sensitivity from 39.5% to 81.0%
Rubin et al. (2005)		CAD improved mean sensitivity from 50% (individual reads) or 63% (double reads) to 76%.
Marten et al. (2004)	18	CAD improved AUC from 0.71 to 0.93 (experienced reader), and from 0.49 to 0.79 (inexperienced reader)
Beigelman-Aubry et al. (2009)	54	CAD improved sensitivities of two readers by 9.6% and 23%
Brown et al. (2005)	8	CAD improved mean detection rates from 64.0% to 81.9%
Das et al. (2006)	25	CAD increased mean sensitivity from 76% to 85%
Awai et al. (2004)	50	CAD increased mean AUC from 0.64 to 0.67

Note: AUC, area under curve.

not have a uniform solid structure. This includes nodules with low density (e.g., ground glass nodules), nodules with a complex appearance (e.g., cavitatory nodules or nodules with irregular matrices), or nodules located close to other dense structures (e.g., juxta-vascular and juxta-pleural nodules). The application of lung CAD systems in patients with co-existing lung disease (e.g., pleural effusions or interstitial lung disease) also remains a challenge as these pathologies obscure underlying nodules. The continued improvement of multidetector CT scanner technology, with the associated decreases in scan times, have reduced the impact of respiratory or cardiac motion artifacts in CT data which previously affected CAD applications.

Other areas of on-going work in lung CAD applications include the diagnosis of pulmonary embolism (Zhou et al., 2005), detection and quantification of pneumothorax (Sanada et al., 1992), quantification and characterization of interstitial lung disease (Katsuragawa et al., 1988; Arzhaeva et al., 2007), and the incorporation of multimodality information (e.g., PET and CT) to further characterize lung lesions (Nie et al., 2006).

15.6.3 Abdominal Imaging

Colorectal cancer is the third most common cancer in both men and women. As the majority of such cancers develop over a period of time from small polyps, the detection of colonic polyps has become a key focus of reducing the morbidity and mortality from colorectal cancer. CT colonography (CTC) is an emerging technique for the detection of colonic polyps and active research and evaluation of CAD for polyp detection in CTC is underway (Yoshida and Dachman, 2005; Bielen and Kiss, 2007).

While commercial CAD systems for CTC polyp detection are already available, at the time of writing, major efforts continue to be directed at obtaining full FDA approval for CAD for CTC polyp detection. Workstations used in the evaluation of CTC studies are capable of displaying data in 2D multiplanar reconstruction views and also provide 3D virtual colonoscopic "fly through" endoluminal views. Therefore, CAD systems have been developed for use with these various viewing modes. Such CAD systems have shown good sensitivity both in isolation and as a "second reader" for detection of clinically significant polyps (Summers et al., 2005; Taylor et al., 2006; Petrick et al., 2008). However, more research is required to properly evaluate the performance and determine the optimal role of CAD in CT colonography. To date, no prospective outcome-based trials have been published evaluating the performance of CAD for detection of polyps in CT colonography. A summary of recent studies on CAD utility in polyp detection in CT colonography is given in Table 15.3.

As with other CAD systems, most of the existing CTC CAD systems are designed for use as a "second reader," although one study recently showed that "concurrent reader" application of a CTC CAD system showed better time efficiency and similar detection of polyps more than 6 mm in size when compared to a "second reader" application (Taylor et al. 2008).

TABLE 15.3 Summary of Results of Recent Studies Evaluating CAD Impact on Detection of Polyps by Radiologists for CT Colonography Studies

Investigators (Year)	Number of CT Exams	Results
Taylor et al. (2009)	50	CAD increased per-patient sensitivity from 82% to 87% for polyps 5 mm or larger
Petrick et al. (2008)	60	CAD increased average reader sensitivity by 15% for polyps 6 mm or larger
Baker et al. (2007)	30	CAD improved average sensitivity for polyp detection from 81.0% to 90.8%
Mang et al. (2007)	52	CAD increased sensitivity from 91% to 96% (expert readers) and from 75.5 % to 93% (nonexpert readers).
Halligan et al. (2006)	107	Polyp detection increased significantly with CAD; on average 12 more polyps detected per reader

Current challenges for CAD for CTC include the variable appearance of the colon (air-filled vs fluid-filled segments, residual fecal material, numerous mucosal folds), the need to integrate information from both supine and prone data sets, the detection of sessile polyps which do not conform to the typical polypoidal shape, and the use of fecal tagging and digital bowel cleansing.

15.6.4 Others

The potential applications of CAD in medical image interpretation are innumerable and continue to grow rapidly. The following are some additional examples of clinical scenarios where the use of CAD has been studied.

15.6.4.1 Cardiovascular Imaging

Within the field of cardiovascular imaging, CAD has been employed in the interpretation of myocardial perfusion SPECT studies (Garcia et al., 2001), the detection and evaluation of plaques on cardiac CT (Dey et al., 2006), and the detection of coronary artery stenoses on CT (Reimann et al., 2009).

15.6.4.2 Neuroradiology

CAD has been studied in the diagnosis of Alzheimer's disease (Brewer et al., 2009; Chaves et al., 2009), assessment of brain CTs done for head trauma (Yuh et al., 2008), detection of intracranial aneurysms on magnetic resonance angiography exams (Uchiyama et al., 2005; Arimura et al., 2006; Yang et al., 2009), detection and evaluation of ischemic brain lesions (Uchiyama et al., 2007; Yamashita et al., 2008), detection of brain tumor invasion (Jensen and Schmainda, 2009), detection of changes in brain tumor status on MRI (Patriarche and Erickson, 2007), and Q4
detection of small acute intracranial hemorrhages on CT (Chan and Huang, 2008).

15.6.4.3 Pediatric Imaging

In pediatrics, the use of CAD has been evaluated in the assessment of bone age based on skeletal radiographs (Pietka et al., 2001), identification of pulmonary nodules in pediatric oncologic patients (Helm et al., 2009), detection of childhood pneumonia on chest radiographs (Oliveira et al., 2008), and detection of therapy-induced leukoencephalopathy in pediatric leukemia patients (Glass et al., 2006). Beyond pediatric radiology, CAD has also been used in the prognostication of neuroblastoma based on digitized histological images (Sertel et al., 2009).

15.6.4.4 Musculoskeletal Imaging

CAD has also been used in the evaluation of bones and joints. Examples include the assessment of disease progression in arthritis (Duryea et al., 2000; Shamir et al., 2009), evaluation of cartilage lesions on MRI (Lee et al., 2004), detection of meniscus tears on MRI knee images (Ramakrishna et al., 2009), analysis of joints spaces in the hand (Pfeil et al., 2007), detection of vertebral body fractures on plain radiographs (Kasai et al., 2006), and change detection on successive bone scan images (Shiraishi et al., 2007).

15.7 Future of CAD

The past four decades have seen a quantum leap in the field of CAD in radiology. Although much has been achieved so far in the field of computer assisted evaluation of medical images, there is still some way to go before achieving widespread acceptance of routine CAD utility in medical image interpretation. The following are key areas that are expected to feature prominently in the field of CAD systems in the coming years.

15.7.1 Broadening the Scope of CAD Systems

Current CAD systems generally focus on highly specific tasks such as the detection of breast microcalcifications or colonic polyps in a screening context. Hence, such CAD systems cannot be applied to the wide range of scenarios presented to physicians in routine practice.

Future CAD systems may come as a "clinical package" to allow more general application of CAD technology to the daily practice of radiology (Doi, 2007). For example, a future "chest imaging CAD scheme" may include detection algorithms for nodules, interstitial lung disease, cardiomegaly, bone density, vertebral fractures, pneumothorax, pleural effusions and interval changes, along with computerized classification of benign and malignant nodules and differential diagnosis of interstitial lung diseases. CAD systems, in addition to detecting lesions and providing differential diagnoses, could also automatically trawl vast image databases for similar-appearing lesions with confirmed diagnoses. Such visual comparisons would facilitate the final diagnosis by a physician.

15.7.2 Developing Multimodality Evaluation

In the process of evaluating medical images, radiologists already routinely process information from different imaging modalities in order to arrive at a diagnosis for a particular patient. Furthermore, with the rapid advances in molecular imaging, fusion imaging techniques such as PET-CT, SPECT-CT, SPECT-MR, and PET–MRI are likely to become more common in future. Enhancement of CAD systems to incorporate information from various imaging modalities (e.g., combining features from mammography, breast ultrasound, and breast MRI) may further increase diagnostic accuracy for an individual patient.

15.7.3 Optimizing the Human–Machine Interface

More work is required in the field of human interaction with CAD systems, which will evolve with time in line with technological advances as humans become more familiar with computer-aided decision making. This key area of usability is critical to the successful incorporation of CAD into the practice of medical image interpretation. CAD systems which require a radiologist to move to a separate workstation to use the detection or diagnostic algorithms are much less likely to be accepted compared to a CAD system which is incorporated into an existing RIS-PACS system. The manner in which CAD outputs are displayed (e.g., as key images in a separate series, or incorporating the CAD markings into the original series as annotations) is also an area where further enhancements are required. Apart from the mode of presentation, the amount of information displayed by the CAD system needs to be carefully considered, as overwhelming the display with too many annotations will likely result in the CAD outputs being ignored by the user. Future CAD systems may be customizable according to the clinical scenario and experience level of the radiologist.

15.7.4 Standardizing Evaluation and Validation of CAD

Current studies on the clinical utility of CAD systems have variable designs. Studies evaluating the clinical value of CAD can often be classified as either sequential reading studies or historical comparison studies. In the sequential reading design, radiologist performance for the same patient cohort is assessed before and after the introduction of CAD. For the historical comparison design, the performance of groups of radiologists over two periods of time are compared, and the patient cohorts and radiologists involved may not be identical for the two time periods. Beyond validation of clinical utility, further studies aimed at determining the impact of CAD on patient outcomes (e.g., improvements in survival) should also be performed to firmly establish the case for CAD in medical image interpretation.

Standardization of CAD evaluation may include clear definitions of task, patient populations, reader training with CAD, study designs, selection of ground truth, data analysis methods, identification of biases, and endpoints for assessment of success or failure. The creation of standardized image databases for different pathologies will allow different CAD systems compared against each other in an objective and reproducible manner. Such databases will also ensure that CAD systems are tested and validated across a variety of image-producing equipment and patient populations before being used in clinical practice.

15.7.5 Managing Legal Implications

As the performance of CAD systems improves, their utility in the image interpretation process may become part of the minimum standard of care. It is therefore plausible that future radiological practices could include CAD as a routine screening for all images before reports are finalized, no different from the current practice of applying "spell-check" algorithms to documents. In such a scenario, it will be necessary to decide how much of CAD information, if any, should be finally incorporated into the medical record of the patient. CAD has already been used by both plaintiff and defense lawyers to make their cases in court (e.g., mammography), a practice which could become routine in future.

15.8 Summary and Conclusion

There is increasing interest in the use of computers to facilitate any or all of the steps in medical image interpretation such as detection, description, diagnosis, and prognosis. For such CAD systems and processes to succeed, it is critical to combine physicians' clinical acumen with the technological capabilities of computers in the appropriate patient context. Key future challenges include optimizing the user interface and establishing standardized methods of evaluating these systems of disease detection and diagnosis. With extensive on-going research efforts, CAD systems will continue to evolve and improve, and are expected to become an integral part of medical image interpretation in the near future.

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